

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761164Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761164
PDUFA Goal Date	November 13, 2020
OSE RCM #	2020-518
Reviewer Name(s)	Donella Fitzgerald, PharmD
Team Leader	Naomi Boston, PharmD
Acting Deputy Division Director	Doris Auth, PharmD
Review Completion Date	October 14, 2020
Subject	Evaluation of Need for a REMS
Established Name	Sutimlimab
Trade Name	Enjaymo
Name of Applicant	Bioverative Therapeutics
Therapeutic Class	Classical complement inhibitor
Formulation(s)	1100/22 mg/mL (50mg/mL) injection, single use vial
Dosing Regimen	Proposed: 6.5 g (patients \geq (b) (4) and < 75 kg) or 7.5 g (patients \geq 75 kg), once per week for the first two doses followed by every other week dosing

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Enjaymo (sutimlimab) is necessary to ensure the benefits outweigh its risks. Bioverativ Therapeutics (Bioverativ) submitted a Biologic Licensing Application (BLA) 761164 for sutimlimab with the proposed indication for treatment of hemolysis in adult patients with Cold Agglutinin Disease. The risks associated with sutimlimab are serious infections and possible autoimmune disease development or worsening. The applicant did not submit a REMS with this application but proposed voluntary dissemination of a prescriber guide and Medication Guide.

Based on the safety profile and the efficacy demonstrated in the pivotal trial, the Division of Risk Management and the Division of Non-malignant Hematology have determined that a REMS is not necessary to ensure the benefits of sutimlimab outweigh its risks.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Enjaymo (sutimlimab) is necessary to ensure the benefits outweigh its risks. Bioverativ submitted a Biologic Licensing Application (BLA) 761164 for sutimlimab with the proposed indication for the treatment of hemolysis in adult patients with Cold Agglutinin Disease (CAD). This application is under review in the Division of Non-malignant Hematology (DNH). The applicant did not submit a REMS with this application but proposed voluntary dissemination of a prescriber guide and Medication Guide.

2 Background

2.1 PRODUCT INFORMATION

Sutimlimab, a new molecular entity,^a is a humanized IgG4 mAb that inhibits Complement Pathway (CP)-specific serine protease, complement component 1 (C1), s subcomponent (C1s).¹ The proposed indication is for treatment of hemolysis in adult patients with CAD. The Applicant's proposed dosage is 6.5g (patients ≥39kg and <75kg) or 7.5g (patients ≥75kg) to be administered by intravenous (IV) infusion over 1-2 hours once per week for the first two doses, followed by every other week dosing thereafter.^b The 50mg/mL injection will be supplied in a single use vial.

Sutimlimab was granted Orphan Drug Designation for autoimmune hemolytic anemia (including CAD). Breakthrough Therapy Designation for the treatment of hemolysis in patients with primary CAD was also granted. Sutimlimab is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761164 relevant to this review:

- 07/27/2016: Orphan Drug Designation granted for autoimmune hemolytic anemia.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug*

- 05/17/2017: Breakthrough Therapy Designation granted for the treatment of hemolysis in patients with primary CAD.
- 09/05/2019: Part 1 of 3 rolling review for BLA 761164 submission for treatment of hemolysis in adult patients with CAD received.
- 02/26/2020: Part 2 of 3 rolling review received.
- 03/13/2020: Part 3 of 3 rolling review received.
- 9/21/2020: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for sutimlimab.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Cold Agglutinin Disease is a rare form of autoimmune hemolytic anemia characterized by lysis of red blood cells induced by immunoglobulin M antibodies (called cold agglutinins) preferentially at lower-than-core body temperature.² The cold agglutinins cause red blood cell agglutination and activate the classical complement pathway via the C1 complex, triggering a cascade of events that result predominately in extravascular hemolysis. CAD is a rare disease, with an estimated incidence of approximately 16 per million.^{3c}

Patients with CAD exhibit varying levels of chronic, ongoing complement mediated hemolysis interspersed with episodic hemolytic flares.⁴ The flares result in varying levels of anemia and anemia-associated signs and symptoms such as fatigue, shortness of breath, lightheadedness and general weakness.⁵ These symptoms are often exacerbated by the advanced age of the population, which is largely ≥ 60 years old.⁶

Similar to other hemolytic disorders, CAD patients with laboratory evidence of hemolysis experience an increased risk of thromboembolic events, including potentially life-threatening events, such as pulmonary emboli and stroke.^d

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are no pharmacological therapies approved for the treatment of CAD. Treatment focuses on minimizing cold-induced symptoms, managing anemia, reducing IgM antibody production and addressing underlying disease.

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Avoidance of cold temperatures helps to minimize red blood cell agglutination and extravascular hemolysis that can result in anemia. Patients should avoid cold environments and ingestion of cold foods and liquids. In the inpatient setting, IV solutions and blood products should be warmed before infusion.

Mild, asymptomatic anemia in CAD patients may not require immediate treatment. CAD patients with severe or symptomatic hemolytic anemia require medical intervention which can include plasmapheresis, intravenous immune globulin therapy or transfusions.⁷ Antibiotics or antivirals are also indicated for hemolysis precipitated by infection.

Therapies used to reduce IgM antibody production vary dependent upon the presence of an underlying lymphoid malignancy. Hemolytic anemic patients with malignancy are recommended for cytotoxic chemotherapy. Those without underlying malignancy may be prescribed rituximab or bortezomib, which are used to suppress the population of lymphocytes that may be producing the IgM.⁸ Rituximab is indicated for the treatment of adults with Non-Hodgkin's Lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis and moderate to severe pemphigus vulgaris. It has a boxed warning for fatal infusion-related reactions, severe mucocutaneous reactions, Hepatitis B virus reactivation and Progressive Multifocal Leukoencephalopathy.⁹ Bortezomib is indicated for use for multiple myeloma and mantle cell lymphoma for patients who have received at least one prior therapy. It does not have a boxed warning, but labeling includes warning and precautions for peripheral neuropathy, hypotension and multiple toxicities which include cardiac, pulmonary, hepatic and embryo-fetal.¹⁰

The use of eculizumab to treat CAD was studied in a prospective phase 2 trial. According to the trial results, eculizumab therapy produced improvement of CAD.¹¹ The improvement is hypothesized to have resulted from eculizumab's complement inhibition properties. Eculizumab is approved for use in patients with paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, myasthenia gravis and neuromyelitis optica spectrum disorder in specific populations. The label includes a boxed warning for serious meningococcal infections, for which a REMS is required to mitigate the risk.¹²

4 Benefit Assessment

Study Design

The pivotal trial (Study BIVV009-03 Part A, NCT03347396) supporting this application was a 26-week, open-label, single-arm, multicenter phase 3 study designed to evaluate the efficacy, safety and tolerability of sutimlimab in 24 patients with CAD with hemoglobin levels ≤ 10.0 g/dL and a recent history of blood transfusion (defined as at least one transfusion during the last six months prior to enrollment). Patients received an IV infusion of study drug over approximately 60 minutes on Day 0, 7 and every 14 days thereafter through Week 25. The primary endpoint was the percent of patients who met the criteria of the responder definition between weeks 5 to 26. The criteria were met if the patient

did not receive a blood transfusion from weeks 5-26, did not receive treatment for CAD beyond what was permitted per protocol^e and the hemoglobin level met either of the following conditions:

- Hgb \geq 12 g/dL at treatment endpoint (mean value of weeks 23, 25, and 26), or
- Hgb \geq 2g/dL from baseline

Part B of Study BIVV009-03 is the ongoing extension study. It will evaluate the long-term safety, tolerability and durability of sutimlimab response in patients who completed Part A.

Results

There were 17 (70.8%) patients that remained transfusion free from Week 5 to 26. At the treatment assessment endpoint, 9 (37.5%) patients had normalized hemoglobin (\geq 12 g/dL), 15 (62.5%) patients had a \geq 2 g/dL increase in Hgb and 15 (62.5%) patients had either $>$ 2 g/dL increase or normalization of Hgb. Based on the responder definition, 13 (54%) patients met the composite primary endpoint criteria. The lower bound of the response rate was $>$ 30% (54.2%, 95% CI: 32.8 to 74.4).¹³

The clinical reviewer concluded that sutimlimab demonstrated efficacy in the treatment of hemolysis in adult patients with Cold Agglutinin Disease.¹⁴

5 Risk Assessment & Safe-Use Conditions

Throughout the clinical development program, a total of 162 patients were treated with sutimlimab in five clinical studies. The primary safety population is comprised of 34 patients with CAD from the following studies:

BIVV009-03 Part A - pivotal phase 3, open-label, single-arm study in patients with primary CAD with a recent history of blood transfusion

BIVV009-03 Part B - ongoing extension study for BIVV009-03 Part A

BIVV009-01 (NCT02502903) Part C – phase 1, open label, multiple-dose study in patients with complement mediated disorders, including CAD, bullous pemphigoid, warm autoimmune hemolytic anemia and antibody mediated rejection in kidney transplant recipients

BIVV009-01 Part E – phase 1, open label, multiple-dose study in patients with CAD previously treated with sutimlimab within a clinical trial or named patient program

5.1 SERIOUS ADVERSE REACTIONS

One death due to hepatic cancer (progressive carcinoma) was reported in a 77-year-old male patient that was discontinued from Study BIVV009-03 Part A on Day 22 and subsequently died on Study Day 32.

^e Concomitant use of rituximab, eculizumab, systemic immunosuppressive agents and systemic corticosteroids $>$ 10 mg prednisone (or its equivalent) per day was prohibited.

The hepatic cancer death was identified as unrelated to study drug by the investigator. The clinical review agrees with this determination.¹⁵

Other serious treatment emergent adverse events are summarized in Table 1.¹⁶

Table 1: Pooled Safety Population – Most common (>5%) TEAEs Grade ≥ 3

FDA Medical Query	BIVV009-01 C&E N=10	BIVV009-03 A&B N=24	Total N=34
Infection, all*	2 (20%)	5 (20.8%)	7 (20.6%)
Sepsis	1 (10%)	2 (8.3%)	3 (8.8%)
Infection, bacterial	0 (0%)	2 (8.3%)	2 (5.9%)
Bleeding*	0 (0%)	2 (8.3%)	2 (5.9%)
Anemia	0 (0%)	2 (8.3%)	2 (5.9%)

Source: FDA clinical reviewer

*The following terms were combined

Bleeding includes: gastrointestinal hemorrhage, vitreous hemorrhage

Infection, all includes: urinary tract infection, pneumonia, pulmonary sepsis, erysipelas, streptococcal sepsis, Escherichia sepsis, cholecystitis acute, respiratory tract infection, viral infection

Sepsis includes: pulmonary sepsis, streptococcal sepsis, Escherichia sepsis

Treatment emergent adverse events (TEAE) that lead to discontinuation occurred in two patients. The first was discontinued from the study due to a non-serious TEAE of Waldenstrom's macroglobulinemia, due to worsening of an underlying medical condition. The second patient was discontinued due to gastrointestinal hemorrhage and hepatic cancer. Per the clinical reviewer, both patients with reports of bleeding had underlying risk factors, and the two anemia events were reviewed and determined not likely due to sutimlimab.

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Serious Infections

Serious infections, including those caused by encapsulated bacteria, were reported in 20.6% (7) of patients treated with sutimlimab. The infections included sepsis, urinary tract infection, pneumonia, wound infection, erysipelas, respiratory tract infection, viral infection and acute cholecystitis. CAD patients are likely at increased risk of developing infections due to advanced age. Elderly patients are often predisposed to infections due to impaired immune function, anatomic and functional changes and increased exposure to pathogens in long-term care facilities and hospitals.¹⁷ The Applicant's proposed labeling includes a Warning and Precaution to monitor patients for early signs and symptoms of infection. To reduce the risk of acquiring an encapsulated bacterial infection, the draft Prescribing Information instructs providers to vaccinate patients according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with persistent complement

deficiencies. In the clinical development program for sutimlimab, all patients received at least one meningococcal vaccine and at least one streptococcus pneumoniae vaccine in the previous five years, or during study period.

5.2.2 Autoimmune Disease

In the primary safety population, there were two (5.9%) out of 34 patients with possible worsening of a previously diagnosed autoimmune disease. One patient with polymyalgia rheumatica reported pain reoccurrence, persistence and/or worsening during the study (BIVV009-03 Part A), ultimately leading to study discontinuation at day 65. Another patient, with a history of multiple sclerosis (MS), had a MS relapse (optic nerve attack flare) on day 194 of study BIVV009-03 Part B. The flare resolved without further reoccurrence after receiving steroids. It was not determined that these events were directly attributable to sutimlimab, however there is a theoretical risk of autoimmune disease development with inhibition of the classical complement pathway. Sutimlimab inhibits C1s and could, theoretically, contribute to autoimmune disease development. Per the medical officer, *“As there remains a theoretical risk of autoimmunity, and development or worsening of autoimmune disease can be serious and is associated with significant morbidity, autoimmune disease will be listed in the Warnings and Precautions in the USPI”*¹⁸. Additionally, a postmarketing requirement (PMR) will likely be issued to follow the long-term outcomes of autoimmune disease in patients exposed to sutimlimab.

6 Expected Postmarket Use

If approved, sutimlimab will likely be prescribed by hematologists experienced in managing patients with CAD. Administration of the IV infusion will be completed by a healthcare professional in a hospital or infusion center. Home-based IV infusion administered by a home health nurse is also a likely setting for sutimlimab usage. Monitoring for signs and symptoms of infection and autoimmune disease can be done by patients, or their caregivers, post-infusion.

7 Risk Management Activities Proposed by the Applicant

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED], a Medication Guide was submitted as part of product labeling and is under review by DNH and the Division of Medical Policy Programs.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of sutimlimab based on the efficacy and safety information currently available.¹⁹

CAD is a rare form of autoimmune hemolytic anemia characterized by lysis of red blood cells induced by immunoglobulin M antibodies (called cold agglutinins), preferentially at lower-than-core body temperature. The cold agglutins cause red blood cell agglutination and activate the classical complement pathway via the C1 complex, triggering a cascade of events that result in extravascular hemolysis. The benefit of sutimlimab treatment for CAD patients was demonstrated in a single phase 3 trial where the primary endpoint was the percent of patients who met the criteria of the responder definition. Based on the definition, thirteen (54%) patients in the pivotal trial met the composite primary endpoint criteria.

Serious infections, including those caused by encapsulated bacteria, were reported in patients treated with sutimlimab. The Applicant's proposed labeling includes serious infections in the Warnings and Precautions. To reduce the risk of acquiring an encapsulated bacterial infection, the label directs prescribers to vaccinate patients according to the most current ACIP recommendations for patients with persistent complement deficiencies.

Development or worsening of autoimmune disease due to inhibition of the classical complement pathway is a theoretical risk for sutimlimab. A PMR to obtain additional long-term safety data is under consideration, as two patients with possible worsening of previously diagnosed autoimmune disease occurred in the trials. Additionally, autoimmune disease will be included in the Warnings and Precautions of the label. Based on the efficacy and the safety data currently available, the risks associated with sutimlimab do not pose unique considerations for a REMS and can be communicated with labeling. This reviewer is not recommending a REMS for management of the potential risks of sutimlimab therapy.

9 Conclusion & Recommendations

Based on the efficacy and the safety data available, the benefit-risk profile is favorable therefore, a REMS is not necessary for sutimlimab to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

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² Bioverativ. Summary of Clinical Efficacy for sutimlimab, July 8, 2020.

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- ¹⁹Diamond, C. Division of Non-malignant Hematology. Draft Clinical Review for sutimlimab, BLA 761164, October 2, 2020.
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